

Claims

1. A reconstituted cell-free translation system comprising translation factors and tRNA species capable of translating exogeneously added mRNA(s) with highly selective incorporation at each codon to form a peptide product, or a peptidomimetic product when the system includes one or more of the tRNA species charged with a non-naturally occurring amino acid or amino acid analog.
2. The translation system of claim 1 for generating a peptide product, which preparation is substantially free of the translation factors EF-P, W, W2 or rescue.
3. The translation system of claim 1 for generating a peptidomimetic product, including one or more of the tRNA species charged with a non-naturally occurring amino acid or amino acid analog that is incorporated into the backbone of the peptidomimetic product.
4. The translation system of claim 2 for generating a peptidomimetic product, which preparation is substantially free of the translation factors EF-P, W, W2 or rescue.
5. The translation system of claim 2, wherein the amino acid analog is selected from the group consisting of β -cyanoalanine, canavanine, djenkolic acid, norleucine, 3-phosphoserine, homoserine, dihydroxyphenylalanine, 5-hydroxytryptophan, 1-methylhistidine, 3-methylhistidine, allyl glycine (or its alkyne derivative), O-methyl-serine, biotinyl-lysine, biotinyl-cysteine (or other biotin-labelled amino acids) cyclohexylalanine, homoglutamate, D-alanine (or other D-amino acids), N-methyl glycine (or other N-methyl amino acids), epsilon-N-methyl-lysine, and radioisotope derivatives of the 21 natural amino acids or unnatural amino acids.
6. The translation system of claim 1, further including one or more exogeneously added mRNA species.
7. A cell-free translation system comprising translation factors and tRNA species capable of translating exogeneously added mRNA(s) to form a peptidomimetic product, which preparation

- 5 (a) lacks one or more active wild-type amino acyl tRNAs and ability to synthesize said wild-type amino acyl tRNA,
- (b) includes at least one exogenous amino acyl tRNA charged with a non-natural amino acid species or amino acid analog, replacing said inactive tRNA species.
8. The translation system of claim 7, including a plurality of different mRNA species.
- 10 9. A kit comprising: (a) components of the translation system of claim 1, which can be admixed to form the reconstituted cell-free translation system capable of translating exogenously added RNA to form a peptide or peptidomimetic; (b) instructions associated there with.
- 15 10. A kit comprising: (a) components of the translation system of claim 7, which can be admixed to form the cell-free translation system capable of translating exogenously added RNA to form a peptidomimetic; (b) instructions associated there with.
- 20 11. A method for generating a peptide or peptidomimetic comprising:
- (a) providing a cell-free translation system of claim 1;
- (b) contacting the translation system with one or more exogenous mRNA species;
- 25 (c) isolating and/or identifying peptide or peptidomimetic products of the translation system.
12. The method of claim 11, wherein one or more of the tRNA species of the translation system is charged with a non-naturally occurring amino acid or amino acid analog that is incorporated into the backbone of a peptidomimetic product.
- 30 13. The method of claim 11, wherein the method is carried out on a library of at least 100 different RNA species, and peptide or peptidomimetic products are identified or isolated from the translation system based on catalytic or binding activity.
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14. The method of claim 11, wherein the mRNA is generated by in vitro transcription in the translation system.
- 5 15. The method of claim 11, wherein the peptide or peptidomimetic products are formed as a covalent adduct of the exogenous mRNA by which said products are encoded.
- 10 16. The method of claim 11, wherein the translation system is contacted with a library of different exogenous mRNA species to generate variegated population of peptides or peptidomimetics products of at least 10^3 different sequences.
17. The method of claim 16, wherein at least 10^8 different sequences are produced.
- 15 18. A peptide or peptidomimetic identified or synthesize by the method of claim 11.
19. A method for generating a peptidomimetic comprising:
- (a) providing a cell-free translation system of claim 7;
 - (b) contacting the translation system with one or more exogenous mRNA species;
 - 20 (c) isolating and/or identifying peptidomimetic products of the translation system.
20. A method for conducting a drug discovery business, comprising:
- 25 (a) by the method of claim 11, identifying peptide or peptidomimetic products of the translation system having a desired biological activity;
 - (b) validating the biological activity of the peptide or peptidomimetic products identified in step (a) by further in vitro or in vivo assay;
 - (c) conducting therapeutic profiling of products validated in step (b), or further analogs thereof, for efficacy and toxicity in animals; and
 - 30 (d) formulating a pharmaceutical preparation including one or more products identified in step (c) as having an acceptable therapeutic profile.
21. The method of claim 20, including an additional step of establishing a distribution system for distributing the pharmaceutical preparation for sale, and

may optionally include establishing a sales group for marketing the pharmaceutical preparation.

22. A method for conducting a drug discovery business, comprising:

- 5 (a) by the method of claim 11, identifying peptide or peptidomimetic products of the translation system having a desired biological activity;
- (b) validating the biological activity of the peptide or peptidomimetic products identified in step (a) by further in vitro or in vivo assay;
- 10 (c) (optionally) conducting therapeutic profiling of products validated in step (b), or further analogs thereof, for efficacy and toxicity in animals; and
- (d). licensing, to a third party, the rights for further drug development of validated products.

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